

## DOCUMENT INFORMATION PAGE

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Application #(s): IND/BLA #####

<b>Communication Type:</b>	Correspondence
<b>Communication Group:</b>	Pediatric Exclusivity
<b>Communication Name:</b>	Pediatric Written Request
<b>Communication ID:</b>	COR-PEDEX-01

<b>Drafted by:</b>	
<b>Clearance History:</b>	
<b>Finalized:</b>	
<b>Filename:</b>	

<b>Signatory Authority:</b>	Officer Director or Deputy
<b>Use Statement:</b>	Use to send the applicant a 'Written Request for Pediatric Studies.'. This letter can either be sent in response to an applicant's proposed pediatric study request (PPSR) or as an FDA initiated letter.
<b>Notes:</b>	Link this letter to any applicable Proposed Pediatric Study Request (PPSR) or amended PPSR (IND or BLA) and to the initial submission (N-000) for all other BLAs for the biological product filed by the same sponsor or manufacturer or, if known, a related entity, including any applications where the biological product is part of a combination product or where the biological product has a minor structural modification.

Version: 03/21/2017

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**The letter begins on the next page.**



BLA #####; may list IND only if there is no BLA

## WRITTEN REQUEST

### SPONSOR/APPLICANT NAME

Attention: CONTACT NAME

TITLE

ADDRESS

Dear CONTACT:

Reference is made to your DATE Proposed Pediatric Study Request for BIOLOGICAL PRODUCT(S).

This/These study/studies investigate the potential use of NONPROPRIETARY NAME OF BIOLOGICAL PRODUCT in the treatment of PATIENT POPULATION AND INDICATION.

BRIEFLY DESCRIBE THE PUBLIC HEALTH BENEFIT (DISEASE PREVALENCE, LACK OF ALTERNATE THERAPIES, ETC.), INCLUDE INFORMATION ABOUT WHY EFFICACY MUST BE ESTABLISHED IN THE PEDIATRIC POPULATION OR WHY EXTRAPOLATION IS APPROPRIATE. IF STUDIES ARE NOT REQUESTED IN NEONATES, INCLUDE A STATEMENT DESCRIBING THE RATIONALE FOR NOT REQUESTING STUDIES IN NEONATES.

To obtain needed pediatric information on PROPER NAME OF BIOLOGICAL PRODUCT, the Food and Drug Administration (FDA) is hereby making a formal Written Request, pursuant to Section 505A of the Federal Food, Drug, and Cosmetic Act (the FD&C Act), as amended by the Food and Drug Administration Amendments Act of 2007, and pursuant to section 351(m) of the Public Health Service Act (the PHS Act), as amended by the Biologics Price Competition and Innovation Act of 2009, that you submit information from the studies described below.

### COMPLETE AND INCLUDE ALL APPROPRIATE SECTIONS

A. CHOOSE A.1. OR A.2 [NOTE: UNDER PROVISIONS OF THE FD&C ACT, SECTION 505A (A), NONCLINICAL STUDIES MAY BE INCLUDED IN A WRITTEN REQUEST IF NEEDED TO INFORM POTENTIAL SAFETY CONCERNS FOR USE OF THE BIOLOGICAL PRODUCT IN PEDIATRIC POPULATIONS.] SELECT ONE OF THE FOLLOWING STATEMENTS:

#### A.1. INSERT IF ADDITIONAL ANIMAL STUDIES ARE NOT REQUIRED

- *Nonclinical study(ies):*

Based on review of the available non-clinical toxicology, no additional animal studies are required at this time to support the clinical studies described in this written request.

**A.2. INSERT IF ADDITIONAL ANIMAL STUDIES ARE REQUIRED**

- *Nonclinical study(ies):*

Based on review of the available nonclinical toxicology, the following study/studies must be conducted prior to the start of the clinical study/studies described in this written request.

ADD STUDY REQUIREMENT (E.G., JUVENILE ANIMAL TOXICITY STUDY, OR OTHER RELEVANT STUDY TYPE). SPECIFY IF, FOR A GIVEN AGE GROUP, NONCLINICAL TRIALS NEED TO BE COMPLETED BEFORE CLINICAL STUDIES ARE INITIATED.

**B. INSERT IF CLINICAL STUDIES APPLY**

- *Clinical studies:*

*Study 1:* LIST SPECIFIC STUDIES REQUIRED AND DEFINE STUDY DESIGN (E.G., DOUBLE-BLIND, RANDOMIZED, PARALLEL GROUP, SAFETY, AND/OR PK).

*Study 2:* LIST SPECIFIC STUDIES REQUIRED AND DEFINE STUDY DESIGN (E.G., DOUBLE-BLIND, RANDOMIZED, PARALLEL GROUP, SAFETY, AND/OR PK).

**CHOOSE B.1. OR B.2.**

**B.1. INSERT IF EFFICACY CAN BE EXTRAPOLATED**

- Efficacy in INSERT PEDIATRIC AGE COHORT will be supported by INSERT RATIONALE OR REQUIREMENTS FOR EXTRAPOLATION AND THE AGE GROUP FROM WHICH EXTRAPOLATION WILL OCCUR

**B.1. INSERT IF EFFICACY CAN NOT BE EXTRAPOLATED**

- Efficacy in INSERT PEDIATRIC AGE COHORT cannot be extrapolated and will be determined by the studies outlined in the WR.

**SELECT THE FOLLOWING TEMPLATE LANGUAGE WHEN APPROPRIATE TO DEFINE IMPLEMENTATION TIMELINE(S) FOR STUDY(IES) DESCRIBED IN THE WRITTEN REQUEST:**

- The nonclinical studies must be completed prior to the implementation of clinical studies.
- The nonclinical studies must be completed and results reported to the Agency prior to the initiation of clinical studies.
- The PHARMACOKINETIC AND/OR PHARMACODYNAMIC AS APPROPRIATE study(ies) must be completed before the efficacy trial(s) to inform dosing.
- The PHARMACOKINETIC AND/OR PHARMACODYNAMIC AS APPROPRIATE study(ies) must be completed before the efficacy trial(s) to inform dosing. Results of the results of the study(ies) must be reported to the Agency prior to the initiation of additional clinical studies.

INSERT STUDY(IES) must be completed in INSERT AGE COHORT before proceeding in INSERT AGE COHORT in order to better define INSERT WHAT IS TO BE DEFINED.

- Objective of each study:
- Patients to be studied:

- Age group in which study(ies) will be performed: INDICATE SPECIFIC AGE RANGES FOR EACH STUDY
- Number of patients to be studied: INDICATE NUMBER OF PATIENTS FOR EACH STUDY.

*Representation of Ethnic and Racial Minorities:* The studies must take into account adequate (e.g., proportionate to disease population) representation of children of ethnic and racial minorities. If you are not able to enroll an adequate number of these patients, provide a description of your efforts to do so and an explanation for why they were unsuccessful.

- Study endpoints: INSERT A and/or B and/or C and/or D

**A. INSERT IF PHARMACOKINETIC ENDPOINTS ONLY APPLY:**

*Pharmacokinetic Endpoints:*

The pharmacokinetic endpoints for INSERT STUDY # must include INSERT REQUIRED MEASUREMENTS, INSERT TIMING OF ENDPOINTS, MINIMUM FREQUENCY, POPULATION IN WHICH ENDPOINTS SHOULD BE OBTAINED, OTHER.

**B. INSERT IF PHARMACOKINETIC AND PHARMACODYNAMIC ENDPOINTS APPLY:**

*Pharmacokinetic/Pharmacodynamic Endpoints:*

The pharmacokinetic and pharmacodynamic endpoints for INSERT STUDY # must include INSERT REQUIRED MEASUREMENTS, INSERT TIMING OF ENDPOINTS, MINIMUM FREQUENCY, POPULATION IN WHICH ENDPOINTS SHOULD BE OBTAINED, OTHER.

**C. INSERT IF EFFICACY ENDPOINTS APPLY:**

*Efficacy Endpoints:* INSERT ALL THAT APPLY:

- The primary efficacy endpoint will be INSERT PRIMARY ENDPOINT and must be assessed by INSERT EXPECTATIONS FOR METHOD OF ASSESSMENT, MAY INCLUDE SCALES VALIDATED FOR PEDIATRIC POPULATION OF INTEREST
- Important secondary endpoints must include INSERT IMPORTANT SECONDARY ENDPOINTS and must be assessed by INSERT METHOD OF ASSESSMENT, MAY INCLUDE SCALES VALIDATED FOR PEDIATRIC POPULATION OF INTEREST

- Measures of compliance must include INSERT REQUIRED COMPLIANCE MEASURES

**D. INSERT IF SAFETY ENDPOINTS APPLY:**

- Safety Endpoints: **INSERT ALL THAT APPLY:**
  - Safety outcomes must include: INSERT AS APPROPRIATE: ADVERSE EVENTS, TOLERABILITY, VITAL SIGNS, LABORATORY PARAMETERS, GROWTH PARAMETERS AND DEVELOPMENT BASED ON KNOWN AE PROFILE OF PRODUCT AND ANY SPECIFIC PEDIATRIC SAFETY CONCERNS.
  - The following adverse events must be actively monitored: INSERT ADVERSE EVENTS REQUIRING ACTIVE MONITORING AND METHOD FREQUENCY AND DURATION OF MONITORING. All adverse events must be monitored until symptom resolution or until the condition stabilizes.
  - The following adverse events must be captured when spontaneously reported: INSERT AE'S TO BE RECORDED WHEN SPONTANEOUSLY REPORTED
  - A Data Monitoring Committee (DMC) must be included because INSERT REASON(S) FROM LIST BELOW.
    - findings INSERT FAVORABLE RESULT, UNFAVORABLE RESULT, OR "OF FUTILITY" at an interim analysis may ethically require termination of the study before its planned completion;
    - of INSERT PARTICULAR SAFETY CONCERN,
    - of the possibility of serious toxicity with MOIETY OR TREATMENT ;
    - the study is being performed in children, a potentially fragile population;
    - the study is being performed in a population at elevated risk of death or other serious outcomes;
    - the study is large, of long duration, and multi-center

See Guidance: *Establishment and Operation of Clinical Trial Data Monitoring Committees*,

<http://www.fda.gov/downloads/RegulatoryInformation/Guidances/ucm127073.pdf>

- *Known safety concerns and monitoring:*
- *Extraordinary results:* In the course of conducting these studies, you may discover evidence to indicate that there are unexpected safety concerns, unexpected findings of benefit in a smaller sample size, or other unexpected results. In the event of such findings, there may be a need to deviate from the requirements of this Written Request. If you believe this is the case, you must contact the Agency to seek an amendment. It is solely within the Agency's discretion to decide whether it is appropriate to issue an amendment.

- *Biological product information:*

- *dosage form*
- *route of administration*
- *regimen*

Use an age-appropriate formulation in the study(ies) described above. If an age-appropriate formulation is not currently available, you must develop and test an age-appropriate formulation and, if it is found safe, pure, and potent in the studied pediatric population(s), you must seek marketing approval for that age-appropriate formulation.

In accordance with section 505A(e)(2), if

- 1) you develop an age-appropriate formulation that is found to be safe, pure, and potent in the pediatric population(s) studied (i.e., receives approval);
- 2) you have unexpired reference product exclusivity or orphan exclusivity to which pediatric exclusivity can attach and the Agency grants pediatric exclusivity, including publishing the exclusivity determination notice required under section 505A(e)(1) of the FD&C Act; and
- 3) you have not marketed the formulation within one year after the Agency publishes such notice, the Agency will publish a second notice indication you have not marketed the new pediatric formulation

If you demonstrate that reasonable attempts to develop a commercially marketable formulation have failed, you must develop and test an age-appropriate formulation that can be prepared by a licensed pharmacist, in a licensed pharmacy, from commercially available ingredients. Under these circumstances, you must provide the Agency with documentation of your attempts to develop such a formulation and the reasons such attempts failed. If we agree that you have valid reasons for not developing a commercially marketable, age-appropriate formulation, then you must submit instructions for preparing an age-appropriate formulation from commercially available ingredients that are acceptable to the Agency. If you conduct the requested studies using such a formulation, the following information must be provided for inclusion in the product labeling upon approval: active ingredients, diluents, suspending and sweetening agents; detailed step-by-step preparation instructions; packaging and storage requirements; and formulation stability information.

Bioavailability of any formulation used in the studies must be characterized, and as needed, a relative bioavailability study comparing the approved drug to the age appropriate formulation may be conducted in adults.

- *Statistical information, including power of study(ies) and statistical assessments:*

- *Labeling that may result from the study(ies):* You must submit proposed pediatric labeling to incorporate the findings of the study(ies). Under section 505A(j) of the FD&C Act, regardless of whether the study(ies) demonstrate that **NONPROPRIETARY NAME OF BIOLOGICAL PRODUCT** is safe, pure, and potent, or whether such study results are inconclusive in the studied pediatric population(s) or subpopulation(s), the labeling must include information about the results of the study(ies). Under section 505A(k)(2) of the FD&C Act, you must distribute to physicians and other health care providers at least annually (or more frequently if FDA determines that it would be beneficial to the public health), information regarding such labeling changes that are approved as a result of the study(ies).
- *Format and types of reports to be submitted:* You must submit full study reports (which have not been previously submitted to the Agency) that address the issues outlined in this request, with full analysis, assessment, and interpretation. In addition, the reports must include information on the representation of pediatric patients of ethnic and racial minorities. All pediatric patients enrolled in the study(ies) should be categorized using one of the following designations for race: American Indian or Alaska Native, Asian, Black or African American, Native Hawaiian or other Pacific Islander or White. For ethnicity, you should use one of the following designations: Hispanic/Latino or Not Hispanic/Latino. If you choose to use other categories, you should obtain agency agreement. **INCLUDE OTHER INFORMATION AS APPROPRIATE**

Under section 505A(d)(2)(B) of the FD&C Act, when you submit the study reports, you must submit all postmarketing adverse event reports regarding this drug that are available to you at that time. All post-market reports that would be reportable under section 21 CFR 600.80 should include adverse events occurring in an adult or a pediatric patient. In general, the format of the post-market adverse event report should follow the model for a periodic safety update report described in the Guidance for Industry E2C Clinical Safety Data Management: Periodic Safety Update Reports for Marketed Drugs and the Guidance addendum. You are encouraged to contact the reviewing Division for further guidance.

Although not currently required, we request that study data be submitted electronically according to the Study Data Tabulation (SDTM) standard published by the Clinical Data Interchange Standards Consortium (CDISC) provided in the document “Study Data Specifications,” which is posted on the <https://www.fda.gov/downloads/ForIndustry/DataStandards/StudyDataStandards/UCM312964.pdf> and referenced in the FDA Guidance for Industry, *Providing Regulatory Submissions in Electronic Format - Human Pharmaceutical Product Applications and Related Submissions Using the eCTD Specifications* at <https://www.fda.gov/downloads/drugs/guidancecomplianceregulatoryinformation/guidances/ucm333969.pdf>.

- *Timeframe for submitting reports of the study(ies):* Reports of the above studies must be submitted to the Agency on or before **INSERT DATE**. Please keep in mind that pediatric exclusivity can attach only to existing exclusivity, if any, that would otherwise expire



nine (9) months or more after pediatric exclusivity is granted, and FDA has 180 days from the date that the study reports are submitted to make a pediatric exclusivity determination. Therefore, if there is unexpired exclusivity that is eligible for pediatric exclusivity to attach, you are advised to submit the reports of the studies at least 15 months (9 months plus 6 months/180 days for determination) before such exclusivity is otherwise due to expire.

If FDA has not determined whether **INSERT BIOLOGICAL PRODUCT** is eligible for reference product exclusivity under section 351(k)(7) of the PHS Act, you may submit a request for reference product exclusivity with supporting data and information to the Agency. Note that neither the issuance of this formal pediatric Written Request, nor any request for exclusivity made by you confers or otherwise implies that you are eligible for reference product exclusivity under section 351(k)(7) of the PHS Act.

- *Response to Written Request:* Under section 505A(d)(2)(A)(i), within 180 days of receipt of this Written Request you must notify the Agency whether or not you agree to the Written Request. If you agree to the request, you must indicate when the pediatric studies will be initiated. If you do not agree to the request, you must indicate why you are declining to conduct the study(ies). If you decline on the grounds that it is not possible to develop the appropriate pediatric formulation, you must submit to us the reasons it cannot be developed.

Submit protocols for the above study(ies) to an investigational new drug application (IND) and clearly mark your submission "**PEDIATRIC PROTOCOL SUBMITTED FOR PEDIATRIC WRITTEN REQUEST STUDY**" in large font, bolded type at the beginning of the cover letter of the submission.

Reports of the study(ies) must be submitted as a biologics license application (BLA) or as a supplement to your approved BLA with the proposed labeling changes you believe are warranted based on the data derived from these studies. When submitting the reports, please clearly mark your submission "**SUBMISSION OF PEDIATRIC STUDY REPORTS - PEDIATRIC EXCLUSIVITY DETERMINATION REQUESTED**" in large font, bolded type at the beginning of the cover letter of the submission and include a copy of this letter. Please also send a copy of the cover letter of your submission to the Office of New Drugs, Immediate Office, Therapeutic Biologics and Biosimilars Team, 10903 New Hampshire Ave, Building 22, Mail Stop 6411, Silver Spring, MD 20993. If you wish to fax it, the fax number is 301-796-9855.

In accordance with section 505A(k)(1) of the FD&C Act, *Dissemination of Pediatric Information*, FDA must make available to the public the medical, statistical, and clinical pharmacology reviews of the pediatric studies conducted in response to this Written Request within 210 days of submission of your study report(s). These reviews will be posted regardless of the following circumstances:



1. the type of response to the Written Request (i.e. complete or partial response);
2. the status of the application (i.e. withdrawn after the supplement has been filed or pending);
3. the action taken (i.e. approval, complete response); or
4. the exclusivity determination (i.e. granted or denied).

FDA will post the medical, statistical, and clinical pharmacology reviews on the FDA website at <http://www.fda.gov/Drugs/DevelopmentApprovalProcess/DevelopmentResources/UCM049872>

If you wish to discuss any amendments to this Written Request, please submit proposed changes and the reasons for the proposed changes to your application. Submissions of proposed changes to this request should be clearly marked "**PROPOSED CHANGES IN WRITTEN REQUEST FOR PEDIATRIC STUDIES**" in large font, bolded type at the beginning of the cover letter of the submission. You will be notified in writing if any changes to this Written Request are agreed upon by the Agency.

Please note that, if your trial is considered an "applicable clinical trial" under section 402(j)(1)(A)(i) of the PHS Act, you are required to comply with the provisions of section 402(j) of the PHS Act with regard to registration of your trial and submission of trial results. Additional information on submission of such information can be found at [www.ClinicalTrials.gov](http://www.ClinicalTrials.gov).

If you have any questions, call **NAME**, Regulatory Project Manager, at **PHONE NUMBER**.

Sincerely,

*{See appended electronic signature page}*

**OFFICE DIRECTOR**

Director

Office of Drug Evaluation **XX**

Center for Drug Evaluation and Research